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| EXAMINER | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/759,416 | ANSARI, ASEEM Z. | |
| | Examiner | Art Unit | |
| | Laura M. Mitchell | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10,13-19,22-28,31,32,34-36 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13-19,22-28,31,32,34-36 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/10/2007 has been entered.

It is noted that claims 1, 13, 22, 31 and 34 have been amended and claims 11-12, 20-21, 29-30, 33 and 37 are canceled in the amendment filed 9/10/2007. Claims 1-10, 13-19, 22-28, 31-32, 34-36 and 38 are under examination.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

It is noted that claims 12, 21, 30 have been canceled and the limitation of "entropically destabilized" has been added to independent claims 1, 13, 22 and 31. Claims 34 and 38 have been amended to clarify the phrase "entropically destabilized" as temperature sensitive.

The rejection of claims 34 and 38 are withdrawn. The limitation of "entropically destabilized" such that the entropy of the linker moiety confers temperature sensitive conditional behavior on the isolated nucleic acid target will be given the broadest reasonable interpretation.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Applicant's arguments and amendments, see REMARKS, filed 9/10/2007, with respect to the rejection(s) of claim(s) 1-10, 13-19 and 31-32 under 35 U.S.C. 102(b) as being anticipated by Ansari et al (2001) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the amendments to the independent claims (see below).

Applicant's arguments, see REMARKS, filed 9/10/2007, with respect to claims 1, 3-4, 8-10, 13, 15, 17-19, 22, 26-28 and 31-32 have been fully considered and are persuasive. Stanojevic and Young do not teach that the length of the linker is at least 30 Å. The rejection of claims 1, 3-4, 8-10, 13, 15, 17-19, 22, 26-28 and 31-32 under 35 U.S.C. 102(a) as being anticipated by Stanojevic and Young has been withdrawn.

Applicant's arguments and amendments, see REMARKS, filed 9/10/2007, with respect to the rejection(s) of claim(s) 22-28 under 35 U.S.C. 102(b) as being anticipated by Ansari et al (2001) as evidenced by Sadowski et al (Nature, 1998, Vol. 335, pages 563-564) have been fully considered and are persuasive. Therefore, the

rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the amendments to the independent claims (see below).

**Claims 1-4, 7-9, 13, 16-19, 31-32, 34-36 and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by Stanojevic (U.S. Patent Application Pub. No. 2003/105045, filed 3/14/2002). The rejection of claims 11, 20, 33, and 37 now cancelled is moot. This rejection is being maintained for reasons of record in the previous Office Action, mailed 6/1/2007 and for reasons outlined below.**

Applicants submit that this rejection has been overcome by amendment to the remaining claims to insert the subject matter of claim 12 into claim 1, the subject matter of claim 21 into claim 13, and the subject matter of claims 33 into claim 31. Applicants submit that since claim 12 was not made subject to this rejection, the rejection of claims 1-4, 8, and 9 has been overcome. Claim 37 has also been amended to recite that the isolated nucleic acid target defines a "sequence-specific" regulatory factor-binding site. Applicants submit that as Stanojevic does not describe a kit having such a nucleic acid target.

**Applicant's arguments filed 9/10/2007 have been fully considered but they are not persuasive.** A factor that can bind to a specific sequence such as a TATA box would meet the limitation of a "sequence specific" regulatory or transcription factor.

Independent claim 1 has been amended to recite a target nucleic acid comprising at least one known or putative binding site for a sequence specific regulatory factor. Stanojevic teaches a construct with five binding sites upstream of TATA box, which is

upstream of a CAT reporter gene (see Figure 6A, in particular). Using the broadest reasonable interpretation of a sequence specific regulatory factor-binding site, the TATA box meets the limitation of a known binding site for a sequence specific regulatory factor, since TATA box binding protein is known to bind the TATA box.

Stanojevic teaches a method for assaying a test compound for activity as a transcriptional effector. Stanojevic teaches that the method includes linking the test compound covalently to a flexible linker domain which is covalently bound to a non-peptidic DNA binding domain to provide a test composition, the DNA (double stranded) binding domain having affinity for a DNA binding site on a DNA template sufficient to bind the site and to modulate transcription at a promoter, contacting the test composition with a transcription mixture including a DNA template, a eukaryotic RNA polymerase molecule capable of forming a complex with the test composition and the DNA template, a buffer and substrates under conditions suitable for RNA synthesis, such that RNA is synthesized. The method further comprises determining the quantity of RNA produced in the presence of the test composition compared to a level in the absence of the test composition, which is a measure of the activity of the test composition as a transcriptional modulator (see paragraph 0021, in particular).

Stanojevic teaches that in at least some embodiments, the flexible linker has a length in the range of 10-100 Å, or a range of 25-40 Å, or a range of 40-60 Å, or a range of 60-100 Å (see paragraph 0011, for example), which meets the limitation of the claimed method in which the linker moiety is at least 30 Å long. Therefore, Stanojevic meets the limitation of a method comprising use of an anchor moiety, a linker moiety

covalently bonded to the anchor moiety, wherein the linker moiety is at least about 30 Å long.

The claimed method recites that the linker is entropically destabilized so that the entropy confers temperature sensitive conditional behavior upon the isolated nucleaic acid target. However, the specification does not provide a specific description of characteristics that an entropically destabilized linker would possess, except for length (see 0161-0162, for example). Since Stanojevic teaches linkers of lengths that meet the claimed limitation of at least 30 Å in length, absent contrary evidence, the linkers would be entropically destabilized so that it would confer temperature sensitive conditional behavior on the nucleic acid target. As written, the claims do not include a step that measures conditional behavior at different temperatures. Therefore, Stanojevic anticipates a method as recited in **claim 1**.

Stanojevic teaches that the natural transcription activator VP16 can be fused to GAL4 increased transcription *in vitro* (see paragraphs 0089-0090, for example). Stanojevic compares activity of artificial transcription factors with that of natural transcription proteins (see paragraph 0040, for example). Therefore, Stanojevic anticipates a method as recited in **claim 13** of evaluating test compounds to identify compounds that facilitate, recruit, or stabilize binding of sequence specific natural transcription factors.

Stanojevic also teaches compositions comprising the artificial transcription factors comprising the test compound covalently attached to a flexible linker domain that

is covalently bound to a non-peptidic DNA binding domain (see paragraph 0022, for example), which meets the limitation of the composition of matter of **claims 31 and 34**.

Stanojevic teaches that the DNA binding domain can be a nucleic acid or peptide nucleic acid or a sequence specific DNA binding natural product (see paragraphs 0013-0014). Stanojevic teaches that the DNA binding domain can also be a triplex forming oligonucleotide (TFO) that binds in the major groove of the DNA helix (see paragraphs 0042-0045), which meets the limitation of the anchor moiety as a major groove-binding/triple helix forming oligonucleotide (**claims 3-4, 9 and 18**). Stanojevic teaches that the DNA binding domain can be a peptide analog such as a polyamide, or sequence specific DNA binding natural product such antibiotics or small organic moieties (see paragraphs 0046), which meets the limitation of the method wherein the anchor comprises a polyamide or an intercalator (**claim 2**).

Stanojevic teaches that the DNA binding domain can be covalently linked to the effector DNA through a flexible linker (see paragraph 0059). Stanojevic teaches that the linker can be a polyglycol, or a plurality of units such as nucleotides, peptides, lower alkyls and other oxygen containing alkyl chain derivatives (see paragraph 0017), which meets the limitation of a method wherein the linker moiety comprising a bifunctional moiety selected from the group consisting of polypeptides, poly(ethyleneglycols), and $C_{1-6}$ alkylenyl, alkenyl, and alkynyl (**claims 7 and 16**) and selected from the group consisting of polypeptides, poly(ethyleneglycols), and $C_{1-6}$ alkyl, alkene and alkyne (**claims 8 and 17**). Absent evidence to the contrary the flexible linker taught by Stanojevic that can be a polyglycol, or a plurality of units such as nucleotides, peptides,

lower alkyls (see paragraph 0059), would meet the limitation of an aptamer. Therefore Stanojevic teaches a method that meets the limitation wherein the linker moiety is an aptamer. The instant specification broadly defines aptamer as a linker moiety that is dimensioned and configured to bind specifically with a small-molecule binding partner. Absent evidence to the contrary, the flexible linker taught by Stanojevic that can be a polyglycol, or a plurality of units such as nucleotides, peptides, lower alkyls (see paragraph 0059), would meet the limitation of an aptamer(**claims 10 and 19**).

Stanojevic also teaches a kit comprising a flexible linker covalently bound to a DNA binding domain and a reactive end group (i.e. a free terminus) that can be used to couple the construct to a test compound of interest to assess the activity of the composition. Stanojevic teaches that the kit would have instructions for using the precursor compound in the disclosed methods (see paragraph 0076, for example). Kits comprising the flexible linker covalently bound to a DNA binding domain and a reactive end group (i.e. a free terminus) would meet the limitation of a kit and composition of matter wherein the bifunctional linker moiety is an aptamer **(claims 32 and 35- 36).**

The claims drawn to kits recite that the linker is entropically destabilized so that the entropy confers temperature sensitive conditional behavior upon the isolated nucleic acid target. However, the specification does not provide a specific description of characteristics that an entropically destabilized linker would possess except for length (see 0161-0162, for example). Since Stanojevic teaches linkers of lengths that meet the claimed limitation of at least 30 Å in length, absent contrary evidence, the linkers would be entropically destabilized so that it would confer temperature sensitive conditional

behavior on the nucleic acid target. Therefore, Stanojevic anticipates the kits as recited in **claim 38.**

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Applicant's arguments see REMARKS 9/10/2007 with respect to claims 1, 3, 8-9, 11, 13, 17-18, 20, 31 and 33 have been fully considered and are persuasive. The rejection of 1, 3, 8-9, 11, 13, 17-18, 20, 31 and 33 under 35 U.S.C. 103(a) as being unpatentable over Felgner et al (U.S. Patent No. 6,165,720) in view of Arora et al has been withdrawn.

**Claims 1-10, 13-19, 31-32 and 34 are rejected under 35 U.S.C. 103(a) as being obvious over Ansari et al (2001, of record) in view of Arora et al (2002 of record). Claims 11, 20 and 33 have been canceled.** Claims 1-10, 13-19, 31-32 and 34 have been newly added to this rejection. This rejection is being maintained for reasons of record in the previous Office Action, mailed 6/1/2007 and for reasons outlined below.

With regard to the previous rejection of the claims under Ansari et al, Applicants submit that the claims as amended do not extend to transcriptional machinery. Claim 1

has been amended to require an isolated nucleic acid target that defines at least one known or putative binding site for a "sequence specific" regulatory factor. Applicants submit that insofar as the transcriptional machinery is not sequence-specific, the claims as amended are clearly distinct from the artificial transcription activator described in the Ansari et al paper. However, as written the claims do not specifically exclude transcriptional machinery. As discussed further below, a factor that can bind to a specific sequence such as a TATA box would meet the limitation of a "sequence specific" regulatory or transcription factor.

Ansari et al teach an artificial transcriptional activator with a polyamide, non-protein DNA binding motif composed of heterocyclic residues that bind to the minor groove of DNA (see page 584, left column, 2nd paragraph, for example), which meets the limitation of an anchor moiety. Ansari et al teach that the polyamide, non-protein DNA binding motif is attached to a flexible polyether linker (i.e. oxygen atoms connected to two alkyl groups) (see page 584, left column, 3rd paragraph, and page 585, Fig 2, for example). Ansari et al teach linkers that are 12 and 36 atoms long (see page 585, Figure 2 legend). Ansari et al teach that the linker attaches the polyamide, non-protein DNA binding motif to an activating region (AH) of approximately 20 residues to form a conjugate (PA-1L-AH) (see page 584, left column, 3rd paragraph, for example), which meets the limitation of a linker moiety covalently bonded to the anchor moiety.

Ansari et al teach that the PA-1L-AH conjugate motif functions in a cell free system, and Ansari et al modified this conjugate motif to try to upregulate transcription. Ansari et al teach that the identity of the activating region was varied by size, identity

and point of attachment to the polyamide. Ansari et al teach that the three activating regions tested were identified as AH, VP1 and VP2 (see page 584, Table 1 and page 587, left column, for example), which meets the limitation of a test compound, bonded to a linker moiety covalently bonded to a polyamide anchor moiety.

Independent claim 1 has been amended to recite that a target nucleic acid comprising at least one known or putative binding site for a sequence specific regulatory factor. Ansari et al teach a plasmid vector with three cognate palindromic sequences upstream of an AdML TATA box, which is upstream of a G-less cassette (see page 591, left column, 2nd paragraph). Using the broadest reasonable interpretation of a sequence specific regulatory factor-binding site, the TATA box meets the limitation of a known binding site for a sequence specific regulatory factor, since TATA box binding protein is known to bind the TATA box. Ansari et al teach that all of the varied conjugates bound to the cognate sites upstream from the AdML promoter (see page 586, left column), which meets the limitation of binding at a point proximate to, but not within the binding site (TATA box).

Ansari et al teach that the activating region is thought to bind to components of the transcriptional machinery that associate with RNA polymerase known as the RNA polymerase II holoenzyme (see page 583, right column). Ansari et al teach that a yeast nuclear extract was used as a reagent for the *in vitro* transcription assays (see page 591 left column section 4.3, in particular), which would comprise a natural transcription factor. Ansari et al teach that substituting the AH activator with VP2 increases the transcriptional activation strength of the conjugate over substitution with VP1 (see page

588, paragraph 2.4, for example), which meets the limitation of a step of contacting *in vitro* the nucleic acid target to a reagent mixture comprising one or more sequence-specific regulatory factors specific for the binding site defined in the nucleic acid target; and then determining whether binding of the sequence-specific regulatory factor to the binding site defined in the nucleic acid target is modulated by presence of the test compound.

**Ansari et al does not specifically teach that the linker moiety is at least 30 Å long and entropically destabilized so that the entropy confers temperature sensitive conditional behavior upon the isolated nucleaic acid target.**

Arora et al teach artificial transcriptional activators comprised of a hairpin polyamide DNA binding domain and a peptide activation domain connected by flexible linkers of various length. Arora et al teach that the activation peptides used were AH and VP2, which have previously shown activation functionality when linked to a hairpin polyamide. Arora et al teach assays to determine the optimal length of the linker region in order to project the activating region away from the DNA in order to increase transcriptional activation. Arora et al teach that the linker plays a role in determining the ability of the activating region to stimulate *in vitro* transcription and that the optimal spacing between the DNA and the activating region is 36-45 Å (see page 13068, right column, in particular), which meets the limitation of a linker moiety that is at least 30 Å in length. Arora et al teach that this knowledge is important in order to be able to design functioning transcription factors.

The claimed method recites that the linker is entropically destabilized so that the entropy confers temperature sensitive conditional behavior upon the isolated nucleic acid target. However, the specification does not provide a specific description of characteristics of an entropically destabilized linker would possess except for length (see 0161-0162, for example). Since Arora et al teach linkers of lengths that meet the claimed limitation of at least 30 Å in length, absent contrary evidence, the linkers would be entropically destabilized so that it would confer temperature sensitive conditional behavior on the nucleic acid target. As written the claim does not include a step that measures conditional behavior at different temperatures.

It would have been obvious to the skilled artisan at the time of the invention to modify the compound taught by Ansari et al and to use a linker that is at least 30 Å in length because Ansari et al teach substitution of a native protein dimerization domain with a various length flexible polylinker in order to modulate the function of a synthetic transcriptional activator (see page 584, left column, 3rd paragraph and page 587, left column, 2nd paragraph, for example) and Arora et al teach that 36-45 Å is an optimal linking region length. The motivation to use a 36-45 Å (at least 30 Å) linking region is the expected benefit of optimized transcriptional activation over the transcriptional activation observed using constructs comprising linking region of shorter or longer length. There is a reasonable expectation of success in using a linking region that is at least 30 Å long to increase transcriptional activation since it has worked previously in the cited reference. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan

would have had a reasonable expectation of success in practicing the claimed invention. Therefore, Ansari et al (2001) in view of Arora et al render obvious a method of evaluating one or more test compounds to identify test compounds that modulate binding of sequence-specific regulatory factors to corresponding single-, double-, or triple-stranded nucleic acid binding sites, as recited in **claim 1**.

Ansari et al teach that the *in vitro* transcription factor assay is performed with a yeast nuclear extract, which would contain natural transcription factors including the RNA Pol II complex. Therefore, Ansari et al (2001) in view of Arora et al render obvious a method to identify test compounds that facilitate, recruit or stabilize binding of sequence-specific natural transcription factors to corresponding single-, double-, or triple-stranded transcription factor binding sites, as recited in **claim 13**.

Ansari et al (2001) in view of Arora et al also render obvious a composition of matter comprising an isolated nucleic acid target that defines a binding site for a sequence-specific regulatory factor, the isolated nucleic acid target having covalently bonded thereto, at a point proximate to the binding site, but not within the binding site, an anchor moiety, a linker moiety covalently bonded to the anchor moiety, wherein the linker moiety is at least about 30 Å long and is entropically destabilized and a test compound conjugated to the linker moiety (**claims 31 and 34**).

Ansari et al teach that the polyamide, non-protein DNA binding motif is attached to a flexible polyether linker (see page 584, left column, 3rd paragraph, and page 585, Fig 2, for example), which meets the limitation of the anchor moiety comprising a polyamide (**claim 2**).

Ansari et al teach a plasmid vector with three cognate palindromic sequences from conjugate binding, upstream of a AdML TATA box (see page 591, left column, 2nd paragraph), which meets the limitation of an isolated target nucleic acid that defines one and only one binding site (TATA) for a regulatory factor, and the nucleic acid target has conjugated or covalently bonded one and only one anchor moiety (**claims 4-5 and 14**).

Ansari et al teach that the DNA binding motif is attached to a flexible polyether linker (i.e. oxygen atoms connected to two alkyl groups) (see page 584, left column, 3rd paragraph, and page 585, Fig 2, for example), meets the limitation of a method wherein the linker moiety is selected from the group consisting of polypeptides, poly(ethyleneglycols), and $C_{1-6}$ alkylenyl, alkenyl, and alkynyl (**claims 7 and 16**) and selected from the group consisting of polypeptides, poly(ethyleneglycols), and $C_{1-6}$ alkyl, alkene, and alkyne (**claims 8 and 17**).

Ansari et al teach attachment of a triplex forming oligonucleotide to a transcriptional activating region upregulated gene expression (see page 584, left column, 2nd paragraph, for example), which meets the limitation of the anchor moiety as a major groove-binding/triple helix forming oligonucleotide (**claims 3, 6, 9, 15 and 18**).

As previously discussed, the instant specification broadly defines aptamer as a linker moiety that is dimensioned and configured to bind specifically with a small-molecule binding partner. Ansari et al teach experiments in which the polyether linker had been conjugated at the C-terminus of the polyamide region, but that conjugation at an internal pyrrole residue is also effective (see page 587, left column, 2nd paragraph and page 589, right column, for example), which meets the limitation of a linker moiety

that has been configured to associate with a binding partner. Therefore the linker rendered obvious by Ansari et al in view of Arora et al also meets the limitation of a method and a composition of matter wherein a linker moiety is an aptamer (claims 10, 19 and 32).

**Claims 22-28 are rejected under 35 U.S.C. 103(a) as being obvious over Ansari et al (2001, of record) as evidenced by Sadowski et al (Nature, 1998, of record) in view of Arora et al ( 2002, of record). Claim 29 has been cancelled.**

Applicants claim a method of evaluating one or more test compounds to identify test compounds that facilitate, recruit, or stabilize binding of sequence- specific transcription factors to corresponding single-, double-, or triple-stranded transcription factor binding sites on nucleic acid, the method comprising the steps of : (a) providing an isolated nucleic acid target that defines at least one desired sequence specific transcription factor binding site, the nucleic acid target having covalently bonded thereto, at a point proximate to, but not within, the transcription factor binding site: (i) an anchor moiety, (ii) a linker moiety covalently bonded to the anchor moiety, wherein the linker moiety is at least about 30 Å long and is entropically destabilized such that entropy of the linker moiety confers temperature-sensitive conditional behavior upon the isolated nucleic acid target and (iii) a test compound bonded to the linker moiety, wherein the test compound is known to modulate binding of natural transcription factors to the transcription factor binding site defined in the nucleic acid target; and then

(b) under transcription conditions, contacting *in vitro* the nucleic acid target of step (a) to a reagent mixture comprising one or more known or putative transcription factors specific for the transcription factor binding site defined in the nucleic acid target; and then (c) determining whether the test compound alters binding of the transcription factor to the nucleic acid target.

The teaching of Ansari et al (2001) and Arora et al are detailed in the rejection above. Ansari et al (2001) in view of Arora et al render obvious a method of evaluating one or more test compounds to identify test compounds that modulate binding of sequence-specific regulatory factors to corresponding single-, double-, or triple-stranded nucleic acid binding sites. However, Ansari et al (2001) and Arora et al do not specifically disclose a method comprising a test compound wherein the test compound is known to modulate binding of a natural transcription factors.

Sadowski et al teach a specific transcriptional activator comprising a DNA binding fragment of the yeast activator GAL4 fused to a portion to the HSV protein VP16. Sadowski et al teach that VP16 activates transcription by binding to host encoded protein that recognized DNA sequence in their promoters. Sadowski et al teach that the acidic portion of VP16 is a very strong transcriptional activator in CHO cells (see page 563, right column, 1$^{st}$ paragraph and page 564, left column). Therefore, VP16 is a transcription activator that can modulate binding of natural transcription factor, such as those that are found in cultured CHO cells. Ansari et al teach that some activating regions tested were tandem repeats of a sequence derived from the viral activator VP16 (see page 584, Table 1 and page 587, left column, for example). Since

Sadowski et al teach that VP16 is known to modulate binding of natural transcription factors, and Ansari et al use portions of VP16, the VP1 and VP2 activating regions used by Ansari et al are test compounds known to modulate binding of natural transcription factors. Therefore, Ansari et al (2001) as evidenced by Sadowski et al in view of Arora et al render obvious a method of evaluating one or more test compounds to identify test compounds that modulate binding of sequence-specific regulatory factors to corresponding single-, double-, or triple-stranded nucleic acid binding sites, comprising a test compound bonded to a linker moiety, wherein the test compound is known to modulate binding of natural transcription factors to the transcription factor binding site defined in the nucleic acid target; as recited in **claim 22**.

Ansari et al teach a plasmid vector with three cognate palindromic sequences from conjugate binding, upstream of a AdML TATA box (see page 591, left column, 2nd paragraph), which meets the limitation of an isolated target nucleic acid that defines one and only one binding site (TATA) for a regulatory factor, and the nucleic acid target has conjugated or covalently bonded one and only one anchor moiety (**claim 23**).

Ansari et al teach that the DNA binding motif is attached to a flexible polyether linker (i.e. oxygen atoms connected to two alkyl groups) (see page 584, left column, 3rd paragraph, and page 585, Fig 2, for example), meets the limitation of a method wherein the linker moiety comprising a bifunctional moiety selected from the group consisting of polypeptides, poly(ethyleneglycols), and $C_{1-6}$ alkylenyl, alkenyl, and alkynyl (**claim 25**) and selected from the group consisting of polypeptides, poly(ethyleneglycols), and $C_{1-6}$ alkyl, alkene, and alkyne (**claim 26**).

Ansari et al teach that attachment of a triplex forming oligonucleotide to a transcriptional activating region upregulated gene expression (see page 584, left column, 2nd paragraph, for example), which meets the limitation of the anchor moiety as a major groove-binding/triple helix forming oligonucleotide (**claims 24 and 27**).

Ansari et al teach experiments in which the polyether linker had been conjugated at the C-terminus of the polyamide region, but that conjugation at an internal pyrrole residue is also effective (see page 587, left column, 2nd paragraph and page 589, right column, for example), which meets the limitation of a an aptamer as defined in the specification as a linker moiety that has been configured to associate with a binding partner. Therefore the method rendered obvious by Ansari et al as evidenced by Sadowski in view of Arora et al also meets the limitation of a method wherein a linker moiety is an aptamer (**claim 28**).

Applicant's arguments with respect to claims 1, 3, 6-9, 13 and 15-18 as rejected under 35 U.S.C. 103(a) as being obvious over Ansari et al (2001, of record) in view of Ansari et al (2002, of record) have been considered but are moot in view of the new ground(s) of rejection below.

**Claims 1, 3, 6-9, 13 and 15-18 are rejected under 35 U.S.C. 103(a) as being obvious over Ansari et al (2001, of record) in view of Arora et al (of record) and further in view of Ansari et al (2002, of record).**

The teaching of Ansari et al and Arora et al has been detailed in the above rejections. As detailed above Ansari et al (2001) in view of Arora et al render obvious a

method of evaluating one or more test compounds to identify test compounds that modulate binding of sequence-specific regulatory factors to corresponding nucleic acid binding sites, as recited in independent claims 1 and 13.

Ansari et al or Arora et al do not teach a method comprising the use of an anchor moiety comprising a peptide nucleic acid (PNA) or a method comprising the use of a linker moiety comprising a bifunctional moiety consisting of polypeptides or polyethylene glycols.

Ansari et al (2002) teach the modular design of synthetic transcription factors in which the two functional modules (DNA binding domain and the regulatory domain) can be exchangeable (see page 765, right column for example). Ansari et al (2002) disclose efforts to replace naturally occurring modules with modules that can display programmable DNA targeting or regulatory activity. Ansari et al (2002) teach that protein DNA binding domains comprising zinc finger binding domains are used to generate binding constructs for specific DNA sequences (page 766, right column), Ansari et al (2002) also teach that triplex-forming oligonucleotide (TFOs) and peptide nucleic acids (PNA) have been used with some success to target specific DNA sequences and are exciting alternatives to peptide DNA binding domains in synthetic transcription factor design (see page 767, left column, 1st paragraph, for example). Ansari et al (2002) teach that the most frequently used DNA binding modules are TFO, PNA and polyamide domains (see page 768, Figure 3 legend, for example). Ansari et al (2002) also teach that the linker is an important variable in optimizing the transcriptional activating function of the construct (see page 769, left column). Ansari et al (2002) teach that while the

linker module for such constructs is usually a flexible or rigid peptide linked by covalent bonds, it can also be substituted with a linker derived from polyethylene glycol without loss of function (see page 768, Figure 3 legend, for example).

It would have been obvious at the time the invention was made to the skilled artisan to use a PNA as a DNA binding domain anchor in a construct comprising a linker domain and a test compound, such as a transcriptional activator domain, in the method rendered obvious by Ansari et al (2001) in view of Arora et al, since Ansari et al (2001) teach that DNA binding motifs can be substituted into a linker/ activator construct in order to increase transcriptional activation and Ansari et al (2002) teach that PNA can be used successfully to target specific DNA sequences. The motivation to use a PNA as a DNA binding domain anchor is the expected benefit of the ability to flexibly design modular transcriptional activators for specific purposes to allow greater control in regulating targeted genes. The development of ligand-responsive synthetic transcriptional activators with tunable potency is desirable to provide graded potency in response to physiological cues. It would also have been obvious to the skilled artisan at the time of the invention to use a polyethylene glycol linker region in the construct because Ansari et al (2002) teach that it is a viable substitute for rigid or flexible peptides in transcriptional activator constructs. The motivation to use a polyethylene glycol linker would be the expected benefit of being able to vary the anchor, linker activator construct for specific use. There is a reasonable expectation of success to use PNA as a DNA binding domain or PEG as a linker since they have been used previously in the cited references. Given the teachings of the prior art and the level of

skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Therefore Ansari et al (2001) in view of Arora et al and further in view of Ansari et al (2002) render obvious a method of evaluating one or more test compounds to identify test compounds that modulate binding of sequence-specific regulatory factors to corresponding nucleic acid binding sites, wherein the anchor moiety comprising a peptide nucleic acid (**claims 3, 6, 9, 15 and 18**) and a method comprising the use of a linker moiety comprising a bifunctional moiety consisting of polypeptides or polyethylene glycols (**claims 7-8 and 16-17**).

Applicant's arguments with respect to claims 22 and 24-27 as rejected under 35 U.S.C. 103(a) as being obvious over Ansari et al (2001, of record) as evidenced by Sadowski et al and further in view of Ansari et al (2002, of record) have been considered but are moot in view of the new ground(s) of rejection below.

**Claims 22 and 24-27 are rejected under 35 U.S.C. 103(a) as being obvious over Ansari et al (2001) as evidenced by Sadowski et al (of record) in view of Arora et al (of record) and in view of Ansari et al (2002).**

The teaching of Ansari et al, Sadowski et al and Arora et al has been detailed in the above rejections. As discussed above Ansari et al (2001) as evidenced by Sadowski et al in view of Arora et al render obvious a method of evaluating one or more test compounds to identify test compounds that modulate binding of sequence-specific

regulatory factors to corresponding nucleic acid binding sites, comprising a test compound bonded to a linker moiety, wherein the test compound is known to modulate binding of natural transcription factors to the transcription factor binding site defined in the nucleic acid target, as recited in claim 22. Ansari et al, Sadowski et al or Arora et al do not teach a method comprising the use of an anchor moiety comprising a peptide nucleic acid (PNA) or a method comprising the use of a linker moiety comprising a bifunctional moiety consisting of polypeptides or polyethylene glycols.

The teaching of Ansari et al (2002) is detailed in the above rejection.

It would have been obvious to the skilled artisan at the time the invention was made to use a PNA as a DNA binding domain anchor in a construct comprising a linker domain and a test compound, such as a transcriptional activator domain, in the method rendered obvious by Ansari et al (2001) as evidenced by Sadowski et al in view of Arora et al, since Ansari et al (2001) teach that DNA binding motifs can be substituted into a linker/ activator construct in order to increase transcriptional activation and Ansari et al (2002) teach that PNA can be used successfully to target specific DNA sequences. The motivation to use a PNA as a DNA binding domain anchor is the expected benefit of the ability to flexibly design modular transcriptional activators for specific purposes to allow greater control in regulating targeted genes. The development of ligand-responsive synthetic transcriptional activators with tunable potency is desirable to provide graded potency in response to physiological cues. It would also have been obvious to the skilled artisan at the time of the invention to use a polyethylene glycol linker region in the construct because Ansari et al (2002) teach that it is a viable substitute for rigid or

flexible peptides in transcriptional activator constructs. The motivation to use a polyethylene glycol linker would be the expected benefit of being able to vary the anchor, linker activator construct for specific use. There is a reasonable expectation of success to use PNA as a DNA binding domain or PEG as a linker since they have been used previously in the cited references. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Therefore Ansari et al (2001) as evidenced by Sadowski et al in view of Arora et al and further in view of Ansari et al (2002) render obvious a method of evaluating one or more test compounds to identify test compounds that modulate binding of sequence-specific regulatory factors to corresponding nucleic acid binding sites, wherein the anchor moiety comprising a peptide nucleic acid (**claims 24, 27**) and a method comprising the use of a linker moiety comprising a bifunctional moiety consisting of polypeptides or polyethylene glycols (**claims 25-26**).

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura M. Mitchell whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Laura McGillem Mitchell
Examiner
11/21/2007

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